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SCHOOL OF PUBLIC HEALTH



**Africa Academy
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Use of Nutritional Supplements During Pregnancy: To V-5 and Calcium Trials

Dr. Alfa Muhihi

Africa Academy for Public Health (AAPH)

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Nutritional Supplementation Studies

Study	Investigators	Design	Intervention	Outcomes
ToV Study	<ul style="list-style-type: none"> ▪ Fawzi, Hunter, Spiegelman, Willet ▪ Msamanga, Manji 	RCT	Vitamin B, C, E and/or Vitamin A	Pregnancy outcomes HIV Progression
ToV-2 Study	<ul style="list-style-type: none"> ▪ Fawzi, Spiegelman, Villamor ▪ Mugusi, Msamanga 	RCT	Vitamin B, C, E (Two dosage regimen)	HIV Progression MTCT of HIV Birth weight, Preterm
PNS	<ul style="list-style-type: none"> ▪ Fawzi, Hunter, Spiegelman, Willet ▪ Manji, Fataki, Msamanga, Urassa 	RCT	Vitamin B, C, E	Fetal loss, LBW, Preterm Maternal Immune status, Hb, Placental weight
Selenium	<ul style="list-style-type: none"> ▪ Fawzi, Kupka ▪ Mugusi, Aboud, Fataki, Matee 	RCT	Selenium	Immune Status Viral load, Mastitis

Nutritional Supplementation Studies....

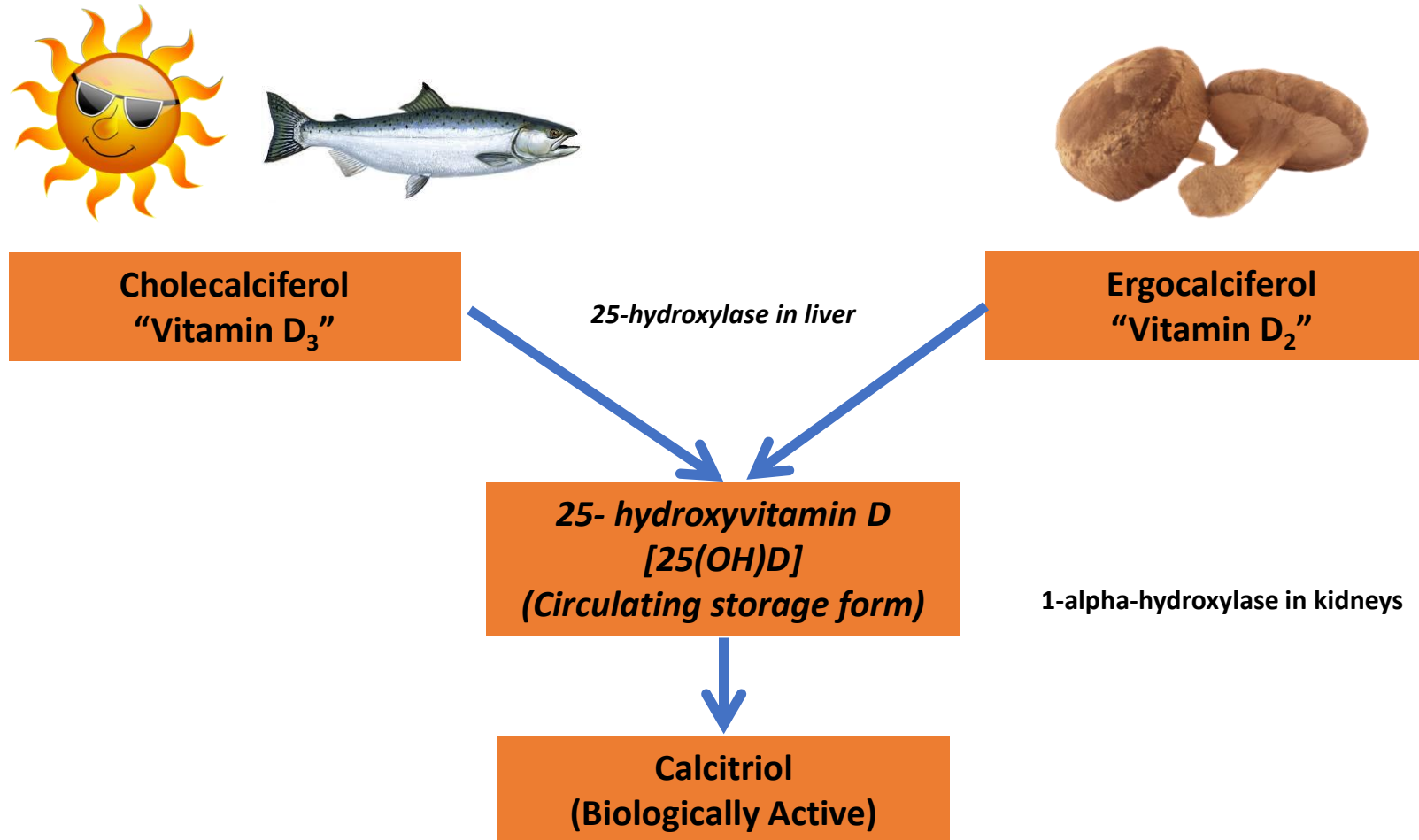
Study	Investigators	Design	Intervention	Outcomes
Malaria - 1	<ul style="list-style-type: none"> ▪ Fawzi ▪ Premji 	RCT	Iron (Safety and efficacy)	Incidence of malaria, Hb, Birth weight
Malaria - 2	<ul style="list-style-type: none"> ▪ Fawzi ▪ Premji 	RCT	Vitamin A Zinc	Placental malaria, Anemia, Low birth weight
TOPPS	<ul style="list-style-type: none"> ▪ Fawzi ▪ Masanja 	RCT	Multivitamin	Compliance, Anemia Weight gain
Familia Salama	<ul style="list-style-type: none"> ▪ Fawzi, Spiegelman, Bärnig-hausen ▪ Chalamila, Sando 	RCT	Community outreach PMTCT option A vs B	Antenatal attendance, Facility delivery, PMTCT
Health Option	<ul style="list-style-type: none"> ▪ Fawzi-Smith ▪ Kaaya Sylvia 	RCT	Integration of mental health care	Depressive disorder and Suicidality at 6 weeks and 9 months

Nutritional Supplementation Studies...

Study	Investigators	Design	Intervention	Outcomes
GCC	<ul style="list-style-type: none"> ▪ Sudfeld, Fawzi ▪ Masanja 	RCT	CHWs intervention	Child development Child stunting
ToV – 5 Study	<ul style="list-style-type: none"> ▪ Fawzi, Sudfeld ▪ Manji, Aboud, Al-beity, Ulenga 	RCT	Vitamin D	Maternal HIV progression SGA, Stunting
Calcium Study	<ul style="list-style-type: none"> ▪ Fawzi, Sudfeld ▪ Pembe, Masanja, Sando, Muhihi 	RCT	Calcium	Pre-eclampsia Preterm

Sources of Vitamin D and Assessment of Status

Primary sources of Vitamin D include sun exposure, oily fish, red meat, liver, egg yolks, fortified foods and supplements



Vitamin D and Infection

- Vitamin D plays a role in innate and adaptive immune responses
 - Alters cytokine production and inhibitory effect on β -cells which is generally *anti-inflammatory*
- Observational studies done in Tanzania have shown low vitamin D is associated with increased mortality, incidence of pulmonary TB, morbidity, weight loss and/or wasting and depression
- RCTs have found vitamin D supplementation reduced incidence of respiratory tract infections in children



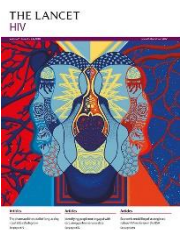
ToV-4 Study

Trial of Vitamin D in HIV Progression and TB Prevention among Adults

Principal Investigators:

Prof. Ferdinand Mugusi

Prof. Wafaie Fawzi



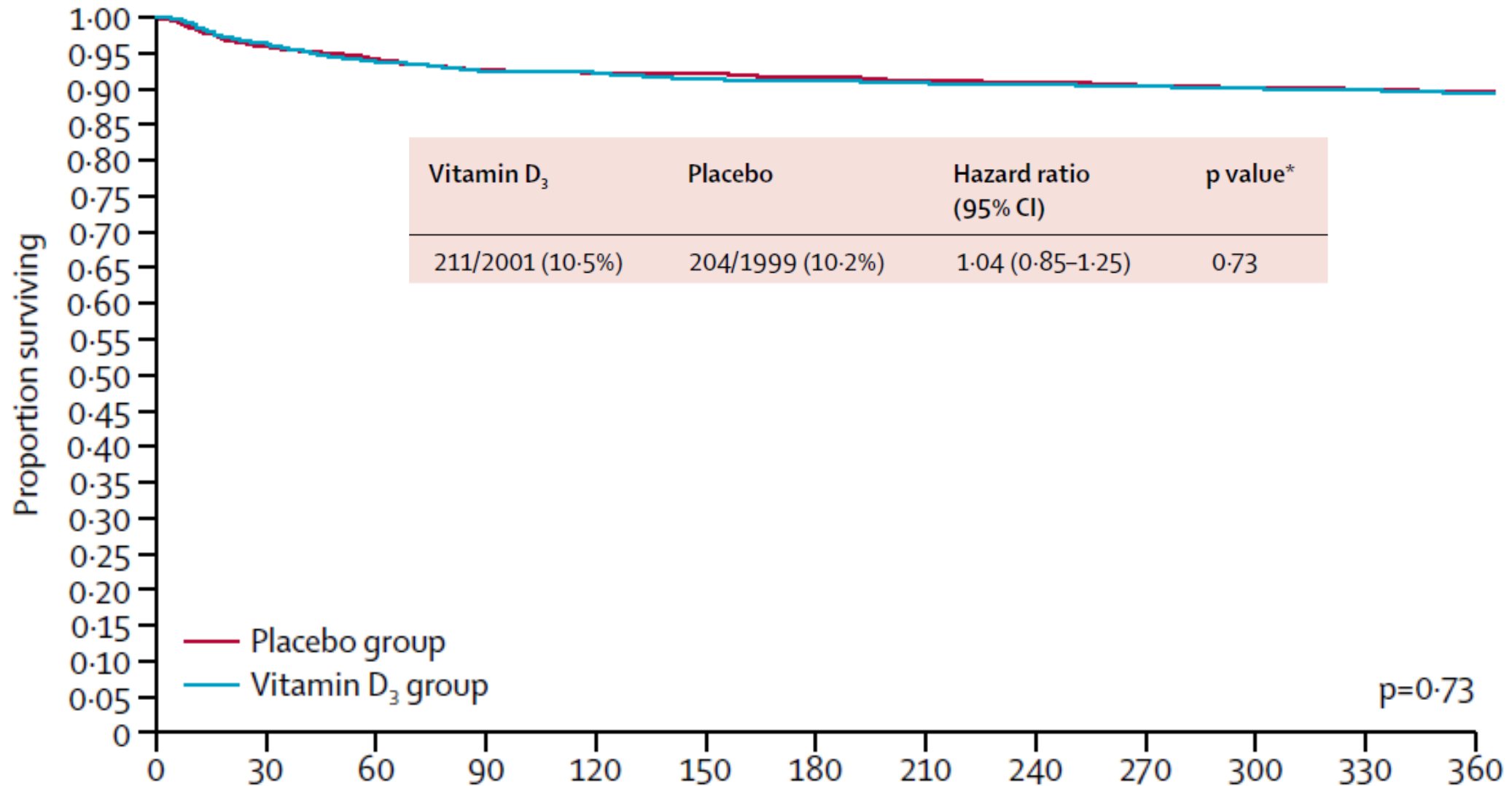
Efficacy of vitamin D₃ supplementation for the prevention of pulmonary tuberculosis and mortality in HIV: a randomised, double-blind, placebo-controlled trial



Christopher R Sudfeld, Ferdinand Mugusi, Alfa Muhihi, Said Aboud, Tumaini J Nagu, Nzovu Ulenga, Biling Hong, Molin Wang, Wafaie W Fawzi

- Location:*** Dar es Salaam, Tanzania
- Participants:*** 4,000 PLWHIV starting ART with low vitamin D (<30 ng/mL)
- Intervention:*** (a) Vitamin D₃ or (b) Placebo Regimen for 12 months
- Primary Outcomes:*** (i) Death and (ii) Incident Pulmonary TB

No Overall Effect of Vitamin D₃ on Mortality



Vitamin D in Pregnancy

- **Observational evidence suggests low 25(OH)D in pregnancy associated with increased risk of**
 - ✓ **Pre-eclampsia**
 - ✓ **Gestational diabetes**
 - ✓ **Low birthweight**
 - ✓ **Small-for-gestational age births**
 - ✓ **Preterm birth**

Ashajafari, et al BMJ 2013
Qin L-L, et al. Nutrients 2016
Tous M, et al. Clin Nutr 2020



ToV-5 Study

Trial of Vitamin D in HIV Progression, Birth Outcomes and Child Health

Principal Investigators:

Prof. Karim P. Manji

Prof. Wafaie Fawzi

Prof. Christopher Sudfeld





ToV-5 Study



- **Study Design**
 - ✓ Randomized, double-blind, placebo-controlled trial of Vitamin D supplements for HIV-infected pregnant women on ART
- **Study Population**
 - ✓ 2,300 HIV-infected pregnant women enrolled 12-27 weeks gestation
- **Randomized Trial Groups**
 - ✓ Vitamin D: Daily 3,000 IU vitamin D3 in pregnancy to 1-year postpartum
 - ✓ Placebo: Daily placebo in pregnancy to 1-year postpartum



ToV-5 Study



- **Primary Outcomes**

- ✓ 1) Maternal HIV progression
 - Increase in WHO disease stage or death
- ✓ 2) Small-for-gestational age births
 - Birthweight <10th percentile
- ✓ 3) Infant stunting at 1 year of age
 - LAZ < -2



ToV-5 Study...



Study Status:

- **Primary trial has been completed**
 - ✓ Primary analysis and manuscript for publication
 - ✓ Results will be out soon
- **Ongoing mechanistic study**
 - ✓ Analysis of samples (analysis of biomarkers)
- **Follow of ToV-5 children**
 - ✓ Assessment of school readiness
 - ✓ Identify areas of intervention

CALCIUM STUDY

Demonstrating Non-Inferiority of Lower Dose Calcium Supplementation During Pregnancy for Reducing Pre-eclampsia and Neonatal Outcomes

Tanzania:

Prof. Andrea B. Pembe

Dr. Honorati Masanja

Dr. Mary Mwanyika Sando

Dr. Alfa Muhihi

Harvard:

Prof. Christopher Sudfeld

Prof. Wafaie Fawzi



Calcium Study...

Background:

- Hypertensive disorders complicate 6-7% of pregnancies; they are a major cause of maternal and perinatal morbidity and mortality in LMICs.
- Calcium supplementation during pregnancy decreases the risk of developing pregnancy-related hypertensive disorders by more than one half. It also significantly reduces the risk of preterm birth.

Calcium Study...



World Health
Organization

Table 1

Suggested scheme for calcium supplementation in pregnant women

Dosage	1.5–2.0 g elemental calcium/day ^a
Frequency	Daily, with the total daily dosage divided into three doses (preferably taken at mealtimes)
Duration	From 20 weeks' gestation until the end of pregnancy
Target group	All pregnant women, particularly those at higher risk of gestational hypertension ^b
Settings	Areas with low calcium intake

^a 1 g of elemental calcium equals 2.5 g of calcium carbonate or 4 g of calcium citrate.

^b Women are regarded as being at high risk of developing gestational hypertension and pre-eclampsia if they have one or more of the following risk factors: obesity, previous pre-eclampsia, diabetes, chronic hypertension, renal disease, autoimmune disease, nulliparity, advanced maternal age, adolescent pregnancy and conditions leading to hyperplacentation and large placentas (e.g. twin pregnancy). This is not an exhaustive list, but can be adapted/complemented based on the local epidemiology of pre-eclampsia.

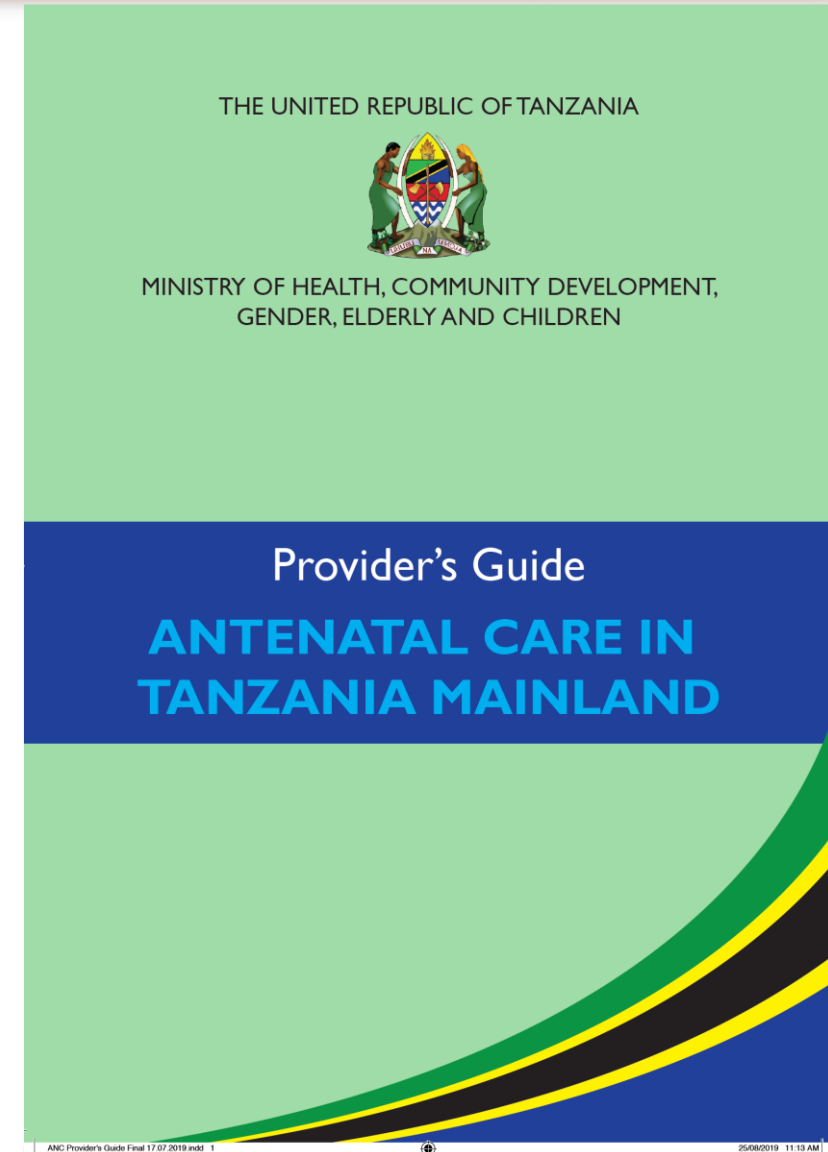


World Health
Organization

Rationale for Calcium Study

WHO recommendation on
Calcium supplementation
before pregnancy for the
prevention of pre-eclampsia
and its complications

WHO recommendation
Calcium supplementation
during pregnancy for the
prevention of pre-eclampsia
and its complications



Rationale for Calcium Study

- Despite its proven efficacy and the WHO recommendation, Calcium supplementation in pregnancy is not yet standard of care in most LMICs
- Barriers to implementing Calcium supplementation in LMICs are;
 - ✓ The cost of the Calcium supplements
 - ✓ Size and weight of Calcium supplements pose transport and storage challenges
 - ✓ **Complexity of the suggested dosing schedule**

Time Period	Supplement Cost
Pre-Pregnancy (6 months x 1 tablet)	USD 3.83
First half of pregnancy (20 weeks x 1 tablet)	USD 2.98
Second half of pregnancy (20 weeks x 3 tablets)	USD 8.95
TOTAL	USD 15.76

Calcium Study Aims

Primary aims:

- To assess if small dose of Calcium supplementation (500mg taken once/day) is equally effective as a WHO recommended dose (500mg taken three times/day) in reducing incidence of pre-eclampsia and preterm births.
- To assess the facilitators, enablers, and barriers to implementation of a 1,500 mg calcium supplement regimen from the perspective of pregnant women and healthcare providers in Tanzanian setting.

Calcium Study Design

TANZANIA

Randomized Trial

Arm A
Standard Dose
1,500mg Ca
N = 5,500

Arm B
Low Dose
500mg Ca
N = 5,500

Observational Cohort

No Calcium supplements
N = 1,000

Implementation Cohort

Standard Dose
1500mg Ca
N = 250

Calcium Study...

Study Participants:

- Primigravida or nulliparous adult women attending RCH clinics before 20 weeks GA in Dar es Salaam

Sample Size:

- Clinical Trial = 11,000 Pregnant Women
- Observational = 1,000 Pregnant Women
- Implementation = 250 Pregnant Women

Calcium Study Status ...

	Enrolled	% of Target
Clinical Trial	10,357	94.2%
Observational Cohort	525	52.5%
Implementation Cohort	-	-

Calcium Study...

- Sister Study in India
 - To compare findings from different settings
 - Make global recommendation easier
- If found to be non-inferior, a lower dose Calcium (500 mg) administered as a single dose, may help overcome challenges
 - ✓ Cost
 - ✓ Dosing complexity and
 - ✓ Logistical (transport and storage)
- Will increase individual and health system adoption of this effective intervention.

thank
you